REMARKS

I. The Office Action

The Office acknowledged Applicants' election with traverse of claims 1-7 for further prosecution as those claims read on an antisense polynucleotide as active agent. The restriction requirement set forth in the Office Action dated January 22, 2008, was made final.

The Office rejected claim 3 under 35 U.S.C. § 112, first paragraph, for assertedly lacking enablement, and under 35 U.S.C. § 112, second paragraph, for assertedly being indefinite. Claim 2 was rejected under 35 U.S.C. § 102(b) for assertedly being unpatentable in view U.S. Patent Publication No. 2003/0083296 (Zhang et al.). Reconsideration of these rejections is respectfully requested.

II. Amendments to the Claims

Claims 3, 5, and 7 have been amended to recite that downregulating expression or activity of caspase-8 is effected by the antisense polynucleotide, the antibody or antibody fragment, or the small interfering RNA (siRNA) molecule. The amendments to claims 3, 5, and 7 are supported by claim 1, as well as claims 3, 5, and 7 previous to the amendment. Claims 63-71 are new. The features of previous claims 3, 5, and 7 are recited in new claims 63, 64, and 68. Claim 65 is supported by the specification at, e.g., page 12, lines 16-19. Claims 66 and 67 are supported by the specification at, e.g., page 13, lines 3-17, and page 14, line 31, through page 15, line 30. Claim 69 is supported by the specification at, e.g., page 11, line 10, through page 12, line 3. Claims 70 and 71 are supported by the specification at, e.g., page 24, lines 2-32, and page 27, line 29, through page 28, line 4. No new matter has been added by way of these claim amendments or additions.

Claims 8-11, 13-24, 26-31, 33-43, 45-47, and 49-62 have been cancelled for being directed to a non-elected invention. Applicants reserve the right to pursue the subject matter of these claims in a divisional application. Claims 2, 3, 5, 7, and 63-71 are pending. Claims 2 and 3, as well as new claims 63, 69, and 71, read on the elected species and are subject to examination.

III. Discussion of Rejection under 35 U.S.C. § 112, first paragraph

Claim 3 was rejected under Section 112, first paragraph, for assertedly encompassing subject matter that is not enabled by the specification. The features of claim 3 are now recited in claim 63. The Office contends that antisense target selection requires a "considerable amount of experimental validation" and, therefore, the use of "untested" antisense oligonucleotides, such as SEQ ID NO: 16, requires an amount of experimentation that is assertedly undue. This rejection is respectfully traversed.

The Office's analysis is flawed in at least two respects. First, the Office asserted that antisense molecules must be "tested" and proven effective (and *validated*) to satisfy Section 112. Section 112, first paragraph, does not require an applicant to provide positive, validated experimental results. Enablement does not hinge on the presence or absence of working examples for each claimed embodiment of an invention. See M.P.E.P. § 2164.02. To satisfy Section 112, first paragraph, an Applicant must only teach one of ordinary skill how to make and use the invention without undue experimentation. See, e.g., M.P.E.P. § 2164.01. Here, the specification identifies caspase-8 as a target for inhibiting hematopoiesis. Applicants provide the nucleotide sequence of the antisense molecule, which is easily produced using standard methods. The specification also discusses routes and timing of administration, and teaches physiological parameters indicative of successful inhibition of hematopoiesis (see, e.g., page 27, line 29, through page 28, line 4; page 29, line 22, through page 30, line 22; and Examples 1-7). To practice the subject matter of claim 3 (now claim 63), one of ordinary skill in the art need only administer the antisense molecule to hybridize with caspase-8 mRNA. In this regard, the Office acknowledged that antisense technology is "advanced" with noted improvements in oligonucleotide delivery and stability techniques (Office Action, page 4). Further, the Examiner speculated that there could be non-specific binding or inefficient downregulation. Non-specific binding is a potential issue associated with antisense technology in general, and has not proven to be an insurmountable obstacle as evidenced by the many successful implementations of antisense technology (see, e.g., specification at page 20, line 23, through page 21, line 6). Additionally, claim 3 (now claim 63) is not limited to "efficient" downregulation. The claim simply recites, indirectly, that hematopoiesis is inhibited, regardless of the efficiency of that inhibition. Thus, any experimentation required to make or use the claimed invention is not "undue," particularly

given that the nucleotide sequence of the antisense molecule is provided. Accordingly, Section 112, first paragraph, is satisfied.

Second, the rejection appears to be based on the premise that target selection also requires a "considerable amount of experimental validation." However, the test of enablement is not whether experimentation is necessary, but whether the experimentation is *undue*. *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976). Indeed, it is well established that "*a considerable amount of experimentation is permissible*" if it is merely routine. *Id.* at 502-04. Any experimentation required to "validate" a target sequence would merely require routine screening assays using well-known laboratory techniques. Thus, even if Section 112 required "validation" (which it does *not*), the "considerable amount" of experimentation asserted by the Office would not be undue.

The specification provides sufficient guidance to enable one of ordinary (relatively high) skill in this well-developed art to make and use the subject matter of claim 3 (now claim 63), which is tailored to the inventors' contribution as described in the specification. Accordingly, Section 112, first paragraph, is satisfied and the rejection of claim 3 (now claim 63) for lack of enablement should be withdrawn.

IV. Discussion of Rejection under 35 U.S.C. § 112, second paragraph

The Office rejected claim 3 for assertedly being indefinite for reciting "a sequence." The rejection is moot in view of the amendment to claim 3 and addition of claim 63. One of ordinary skill in the art would understand the metes and bounds of claim 63; thus, the requirements of Section 112, second paragraph, are satisfied.

V. Discussion of Rejection under 35 U.S.C. § 102(b)

Claim 2 was rejected under Section 102(b) for assertedly being unpatentable in view of U.S. Patent Publication No. 2003/0083296 (Zhang). This rejection is respectfully traversed because the cited reference does not enable a method of inhibiting hematopoiesis.

An assertedly anticipating reference must provide an enabling disclosure to support an anticipation rejection under Section 102. *In re Hoeksema*, 399 F.2d 269, 273 (C.C.P.A. 1968). Zhang does not enable a method of inhibiting hematopoiesis by

downregulating an expression or activity of caspase-8 using an antisense polynucleotide capable of specifically hybridizing with an mRNA transcript encoding caspase-8, as required by the pending claims. Zhang assertedly discloses antisense oligonucleotides that modulate caspase-8 expression. A single published claim (claim 18) recites use of an antisense compound to treat a hematopoietic disorder as "a disease or condition associated with caspase-8" -- there is no other mention of "hematopoiesis" or "hematopoietic disorders" within the publication. Indeed, Zhang does not teach any hematopoietic disorder, much less teach diseases or conditions amenable to treatment by inhibiting expression of caspase-8. Mere naming of claimed subject matter by a cited reference is insufficient under Section 102 if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Res.*, 346 F.3d 1051, 1055 (Fed. Cir. 2003); see also M.P.E.P. § 2121.01. Confusion surrounding Zhang's disclosure is compounded by requiring administration of *either* a therapeutically effective amount *or* a prophylactically effective amount to *treat* the hematopoietic disorder. In context, the prophylactically effective amount must be a non-therapeutically effective amount, which makes little sense if treating a hematopoietic disorder. One of ordinary skill would be led to undue experimentation to find a suitable hematopoietic disorder and then determine the prophylactically effective amount that is not therapeutic but still treats the disorder (disease or condition).

One of ordinary skill could not practice the claimed invention based on the single recitation of hematopoietic disorder in Zhang. Indeed, undue experimentation would be required in the absence of a teaching that caspase-8 plays a role in hematopoiesis in the absence of some particular hematopoietic disorder/disease or condition amenable to treatment by inhibition of hematopoiesis and in the absence of teaching a prophylactically effective amount, different from a therapeutically effective amount, that is useful in treating a hematopoietic disorder (again, without being a therapeutically effective amount). Without such teachings, the ordinary skilled artisan would not have believed that caspase-8 modulation would have any effect on hematopoiesis. In contrast, the present application establishes that inhibition of caspase-8 impairs hematopoietic cell precursors, impairs the capacity of bone marrow cells to expand in spleen, arrests B-cell stimulation, inhibits differentiation of monocyte precursors, and impairs hematopoiesis in mice (see Examples 1-7). In addition to establishing a link between caspase-8 and hematopoiesis, the instant

application provides guidance allowing one of ordinary skill to measure success in practicing the claimed invention (see Examples 1-7). Zhang provides *no guidance* as to how to determine if hematopoiesis is inhibited and the relevant disclosure in Zhang is fatally confused. Because Zhang does not provide an enabling disclosure with respect to hematopoietic disorders, the reference does not anticipate the claimed invention under Section 102.

VI. Conclusion

In view of the foregoing, Applicants believe the pending application is in condition for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the application, the Examiner is invited to contact the attorney listed below.

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Respectfully submitted,

By _____

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